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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,745	09/08/2003	Linda Burkly	CIBT-P02-115	4545

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EXAMINER	
BRANNOCK, MICHAEL T	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,745	BURKLY ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 7-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6 and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *090803,022505*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 9/8/2003 have been entered in full.

Claims 1-16 are pending. Claims 2, 3, 7-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/24/2006.

Applicants election of Group I, as the claims relate to administration of a hedgehog antagonist, drawn to methods of modulating lipid metabolism in an animal comprising the administration of a hedgehog antagonist, wherein the disorder is atherosclerosis, is acknowledged. Applicant asserts that claims 1, 4, 5, 6, and 12-16 read on the elected invention. Applicant traverses the restriction requirement, stating that the a simultaneous examination of both groups, Group I (agonists) and Group II (antagonists), would not impose a significant additional burden on the examiner. This argument has been fully considered but not deemed persuasive. In the instant case, hedgehog antagonists, that were known to cause developmental abnormalities (cyclopamine), were known in the art long before the hedgehog agonists (e.g. hedgehog polypeptide), reviewed in Incardona et al., Development 125(3553-3562)1998. Thus, although a search of any one of the groups may overlap that of another, the search of one group could not be relied upon, solely, to provide art that is anticipatory or would render obvious the invention of any other group, and to search all groups would be burdensome. Therefore, the restriction is maintained and made final.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, 6, and 12-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claims 1, 4, 5, 6, and 12-16 require methods for modulating lipid metabolism, or vacuole formation, etc., comprising the administration of a hedgehog antagonist, yet the claims lack a step, or steps, that lead back to and accomplish the goal set forth in the preamble of the claim, e.g. there is no step in claim 1 for the artisan to follow that accomplishes the recited goal of modulating lipid metabolism. The claim is therefore rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

Claims 1, 4 and 5 recite methods of "modulating" and/or a "lipid modulator", yet the specification does not define the terms "modulating" or "modulator" such that the skilled artisan would unambiguously no what is and what is not encompassed by the claims. At page 5, line 26, the specification defines modulate to mean "regulate according to measure or proportion". However, since "regulate" is also a relative and ambiguous word, this definition does not provide sufficient understanding of the term "modulate". Therefore, the metes and bounds of the claims cannot be determined.

Claim 12 requires a "hedgehog mimetic" or a "anti-hedgehog homolog". These terms render the claim indefinite because they are each relative terms and the specification does not set forth the degree of mimicry or homology which defines the bounds of the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 5, 6, and 12-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims required methods comprising administration of a "pharmaceutically effective amount" of a hedgehog antagonist. The term "pharmaceutically effective amount" implicitly requires that the amount be effective for some form of treatment or therapy. The specification has not put forth a pharmaceutically effective amount of a hedgehog antagonist. The specification describes the use of a hedgehog antagonist resulting in "failure to thrive, runting, and early death" of neonatal mice (page 5). There does not appear to be any evidence of any therapy or benefit resulting in the administration of any amount of hedgehog antagonist. One skilled in the art would not consider the lack of weight gain and peri-natal death experienced by genetically obese mice to be any type of therapy (Figure 4). Applicant's invention has merely poisoned the development of the intestines of these mice, and it is far from clear or certain that such a finding could be used to provide a treatment or therapy for any particular condition. Hedgehog antagonists are old in the art and their effects are well known to

be in opposition to any particular therapy - with the possible exception of treatment of certain cancers, which the claims do not appear to encompass. Cyclopamine is a well-known hedgehog antagonist and it is also well- known to cause hideous deformities in animals and phenocopies hedgehog mutations (see Incardona et al., Development 125(3553-3562)1998, especially page 3553 col 1 and page 3560, paragraph 1), such mutations being known to cause deformities of the intestines in mice (see Chiag et al., Nature 383(407)1996, especially page 408, col 1). While it is true that many useful therapies may have adverse consequences to a fetus, it does not follow that because a treatment has an adverse consequence to a fetus, then it is likely to be a useful therapy. While the details of Applicant's discoveries are of interest scientifically, the specification has not provided sufficient guidance to one highly skilled in the art make a pharmaceutically effective amount of a hedgehog antagonist to be used in any of the claimed methods.

Further, claims 12-14 require anti-hedgehog homologs, e.g. hedgehog "mimetics, modified hedgehog peptides, or inactive hedgehog variants that act as antagonists. The specification has not provided guidance as to which particular hedgehog variants/mimetics could be used. The specification presents only an invitation to the artisan to try to find variants that have the required property of binding a hedgehog receptor but do not elicit a response. Based on the teachings of the specification, the skilled artisan is left to undergo extensive and random trial and error experimentation in order to find variants that have this property. The problem of predicting protein structure sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a

reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions) nor which changes to make to bring about any desired property. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants with the required properties that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Therefore, due to the large quantity of experimentation required to find a pharmaceutically effective amount of a hedgehog antagonist, the lack of direction and guidance provided in the specification, the contrary state of the prior art which establishes that hedgehog antagonism has extraordinarily complex and unpredictable effects on the development of animals

and that such effects on the intestines are contrary to the use of the antagonists as treatments of intestinal disorders (see Chiag et al. and Incardona et al.), it would require undue experimentation on the part of the skilled artisan to make and use the invention as claimed, if in fact, the invention could be used as such.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 12, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Chiang et al., Nature 383(407-413)1996. Chiang et al., disclose that the administration a hedgehog antagonist results in abnormalities in the foregut of developing animals (page 408, col 1). Thus one of ordinary skill in the art practicing the method of Chiang et al. would necessarily accomplish the goal recited in the claim because the methods steps of Chiang et al., e.g. administering a hedgehog antagonist in amount sufficient to disrupt foregut development would necessarily modulate, i.e. disrupt, lipid metabolism in an animal, absent evidence to the contrary.

Conclusion

No claims are allowable.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649. Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

MB

October 14, 2006